UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

18/JUL/2008

MEMORANDUM

Subject:	Name of Pesticide Product:	OD 70 Herbicide
	EPA File Symbol:	264-RNAE
	DP Barcode:	D339753
	Decision No.:	378457
	Action Code:	R01.0
	PC Code:	015804 Thiencarbazone-methyl

From: Rick J. Whiting, Biologist
Technical Review Branch (TRB)
Registration Division (7505P)

To: Hope Johnson, RM Team 25
Herbicide Branch
Registration Division (7505P)

Applicant: Bayer CropScience
P.O. Box 12014, 2 T.W. Alexander Drive
Research Triangle Park, NC 27709

FORMULATION FROM LABEL:

Active Ingredient(s):	% by wt
015804 Thiencarbazone-methyl (CAS No. 317815-83-1]	1.0
Inert Ingredient(s): *	99.0
Total:	100.0%

*Contains Petroleum Distillates

ACTION REQUESTED: The Risk Manager requests: "Bayer CropScience has submitted a new herbicide AI: Thiencarbazone-methyl. This new AI is a Tri-Lateral Review with PMRA and UK. PMRA may be the lead for the acute toxicology of this end-use product, but it may be EPA. This has not been determined yet. This is an end-use product (264-RNAE). Enclosed are the acute toxicology studies, label and CSF. Reviewer will need Circa access for review exchange with UK and PMRA, and must use OECD Tier II template for review."

BACKGROUND: Bayer CropScience has submitted six acute toxicity studies, a Basic Formulation CSF (dated January 15, 2007) and a proposed label to support the registration of OD 70 Herbicide, EPA File Symbol 264-RNAE. The acute toxicity studies were assigned MRID numbers 470702-44 thru -49. The acute oral, dermal, inhalation and primary eye and dermal studies were conducted at Bayer HealthCare AG and the dermal sensitization study at Bayer CropScience. Canada's Pest Management Regulatory Agency (PMRA) conducted the primary review of the studies. TRB performed the secondary review and made changes as necessary.

COMMENTS AND RECOMMENDATIONS:

1. The acute oral, dermal, inhalation and primary eye and dermal studies have been reviewed and classified as Acceptable.

2. The dermal sensitization study was classified as Supplementary for the following reasons:

The 2003 OPPTS harmonized guidelines state the "LLNA is the preferred method, where applicable." The "where applicable" correlates to the performance parameters in the appendix — the 1999 ICCVAM report. In 1999, ICCVAM validated the method using 209 "single compound compounds" but did not validate the assay for mixtures. The appendix clearly states the LLNA should not be used for metals, aqueous solutions, and mixtures. In January 2008, ICCVAM updated the validation report on LLNA regarding mixtures, metals and aqueous solutions. ICCVAM findings are that when compared to the guinea pig it has a false negative rate of 50%, a false positive rate of 44%, and accuracy rate of 53% in mixtures. Due to these limitations, EPA questioned whether the negative result found in this study is correct. EPA decided to perform a weight of the evidence approach for this joint review chemical by obtaining information on each component (inerts ingredient) in this mixture. After reviewing the components sensitization potential, EPA determined that most were non-sensitizers and other components were assumed to be below the sensitizing threshold. Therefore, to avoid further animal testing EPA will classify the study as "supplemental" and recommend label language as a non-sensitizer for BYH 18636 (Thiencarbazone-methyl).

3. The acute toxicity profile for OD 70 Herbicide, EPA File Symbol 264-RNAE, is as follows:

Acute oral toxicity	III	Acceptable	MRID 47070249
Acute dermal toxicity	III	Acceptable	MRID 47070248
Acute inhalation toxicity	III	Acceptable	MRID 47070247
Primary eye irritation	III	Acceptable	MRID 47070246
Primary skin irritation	III	Acceptable	MRID 47070245
Dermal sensitization	Negative	Supplementary	MRID 47070244

4. Based on the toxicity profile above, the following are the precautionary and first aid statements for this product as obtained from the Label Review System:

PRODUCT ID #: 000264-01062

PRODUCT NAME: OD 70 Herbicide

PRECAUTIONARY STATEMENTS

SIGNAL WORD: CAUTION

Hazards to Humans and Domestic Animals:

Contains Petroleum Distillate.

Harmful if absorbed through skin. Harmful if inhaled. Harmful if swallowed. Avoid contact with skin or clothing. Causes moderate eye irritation. [Wear protective eyewear.]* Avoid contact with skin, eyes or clothing. Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, or using tobacco. Wear long-sleeved shirt and long pants, socks, shoes, and chemical-resistant gloves (such as Barrier Laminate, Butyl Rubber, Nitrile Rubber, Viton, Selection Category F). Remove and wash contaminated clothing before reuse. Avoid breathing spray mist.

*[Protective eyewear may be specified, if appropriate]

First Aid:

If on skin: Take off contaminated clothing. Rinse skin immediately with plenty of water for 15-20 minutes. Call a poison control center or doctor for treatment advice.

If inhaled: Move the person to fresh air. If person is not breathing, call 911 or an ambulance, then give artificial respiration, preferably mouth-to-mouth if possible. Call a poison control center or doctor for further treatment advice.

If swallowed: Immediately call a poison control center or doctor for treatment advice. Do not induce vomiting unless told to by a poison control center or doctor. Do not give any liquid to the person. Do not give anything by mouth to an unconscious person.

If in eyes: Hold eye open and rinse slowly and gently with water for 15-20 minutes. Remove contact lenses, if present, after the first 5 minutes, then continue rinsing. Call a poison control center or doctor for treatment advice.

NOTE TO PHYSICIAN: May pose an aspiration pneumonia hazard. Contains petroleum distillate.

Have the product container or label with you when calling a poison control center or doctor or going for treatment. You may also contact 1-800-xxx-xxxx for emergency medical treatment information.

5. The Basic Formulation CSF (dated January 15, 2007) for the proposed product should also be reviewed and accepted by the TRB Chemistry Team.

Reviewer: PMRA
Risk Manager (EPA): 25

Date: July 18, 2008

STUDY TYPE: Acute Oral Toxicity - Rat; OPPTS 870.1100; OECD 423

TEST MATERIAL: BYH 18636 (Thiencarbazone-methyl) [Purity: BYH 18636: 9.98 g/L (Certified by analysis); Batch No. 2006-003517 (EFIM000617); brown liquid]

CITATION: Eiben, R. (2006) BYH 18636 + (Inert Ingredient): Acute Toxicity in the Rat After Oral Administration. Project Number: AT03394, T9077050, M-279810-01-2. Unpublished study prepared by Bayer Ag. 29 p. October 23, 2006. MRID No. 47070249

SPONSOR: Bayer CropScience AG, Alfred-Nobel-Str. 50, 40789 Monheim, Germany

EXECUTIVE SUMMARY: In an acute oral toxicity study (MRID 47070249), groups of three fasted female Wistar rats (strain HsdCpb:Wu) were given an initial single oral dose of 2000 mg/kg body weight BYH 18636 (Thiencarbazone-methyl) [Purity: BYH 18636: 9.98 g/L (Certified by analysis); Batch No. 2006-003517 (EFIM000617); brown liquid] formulated in tap water and observed for at least 14 days. As no mortalities were observed, three additional female rats were treated at the same dose and observed for 14 days.

A dose of 2000 mg/kg body weight was tolerated by female rats without mortalities, toxicological effects on weight gain or gross pathological findings. The clinical signs were decreased motility and piloerection.

According to OECD guideline 423, the LD_{50} cut-off of BYH 18636 (Thiencarbazone-methyl) [Purity: BYH 18636: 9.98 g/L (Certified by analysis); Batch No. 2006-003517 (EFIM000617); brown liquid] is greater than 5000 mg/kg bw. (Category 5 / unclassified of the Globally Harmonized Classification System). According to EPA guidelines, the LD_{50} for the female rats is greater than 2000 mg/kg, resulting in an EPA Toxicity Category III.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. **Test Material:** BYH 18636
   Description: brown liquid
   Lot/Batch #: 2006-003517 (EFIM000617)
   Purity: BYH 18636: 9.98 g/L (Certified by analysis)
   CAS #: CAS No. 317815-83-1

2. **Vehicle and/or positive control:** None

3. **Test animals:** **Rats**
   Species: Wistar
   Strain: HsdCpb:Wu
   Age/weight at dosing: 10-12 weeks / 156-178 g
   Source: Harlan/Winkelmann GmbH, 33178 Borchen, Germany
   Housing: Group caged conventionally in polycarbonate cages
   Diet: "Provimi Kliba 3883.0.15 Maus/Ratte Haltung, Kaiseraugst Switzerland" *ad libitum*
   Water: Tap water *ad libitum*
   Environmental conditions:
   Temperature: 22 ± 2 □C
   Humidity: 55 ± 5 %
   Air changes: ~ 10 changes /hr
   Photoperiod: 12 hrs dark / 12 hrs light
   Acclimation period: 5 days

B. STUDY DESIGN and METHODS:

1. **In life dates** - Start: July 05 2006 End: July 26 2006

2. **Animal assignment and treatment** - Animals were assigned to the test groups noted in Table 1. Following an overnight fast, rats were given a single dose of BYH 18636 (Thiencarbazone-methyl) by gavage then observed several times on the day of administration and subsequently at least once daily and weighed weekly for 14 days. Survivors were sacrificed and a necropsy was performed.

3. **Statistics** - The oral LD_{50} was calculated according to OECD guideline 423.

II. RESULTS AND DISCUSSION:

A. Mortality is given in Table 1. There were no mortalities at a dose of 2000 mg/kg bw.

TABLE 1. Doses, mortality/animals treated

Dose mg/kg bw.	Toxicological result*	Occurrence of signs	Time of death	Mortality (%)
Female				
(1st) 2000	0 / 3 / 3	55' -- 5h	--	0
(2nd) 2000	0 / 3 / 3	2h -- 6h	--	0

* number of animals which died spontaneously or were sacrificed in moribund state / number of animals with signs of toxicity / total number of animals used per group

B. Clinical observations – The following clinical signs were observed: decreased motility and piloerection. These signs were only seen up to 6 hours post dosing.

C. Body Weight – There were no adverse effects on body weights or body weight gain.

D. Necropsy – The necropsies performed at the end of the study revealed no particular findings.

E. Applicant's Conclusions: According to OECD guideline 423, the LD_{50} cut-off of BYH 18636 (Thiencarbazone-methyl) is greater than 5000 mg/kg bw. (Category 5 / unclassified of the Globally Harmonized Classification System). According to EPA guidelines, the LD_{50} for the female rats is greater than 2000 mg/kg, resulting in an EPA Toxicity Category III.

Reviewer: PMRA
Risk Manager (EPA): 25
Date: July 18, 2008

STUDY TYPE: Acute Dermal Toxicity - Rat; OPPTS 870.1200; OECD 402

TEST MATERIAL: BYH 18636 (Thiencarbazone-methyl) [Purity: BYH 18636: 9.98 g/L (Certified by analysis); Batch No. 2006-003517 (EFIM000617); brown liquid]

CITATION: Eiben, R. (2006) BYH 18636 + (Inert Ingredient): Acute Toxicity in the Rat After Dermal Application. Project Number: AT03393, T0077051, M-279812-01-2. Unpublished study prepared by Bayer Ag. 30 p. October 23, 2006. MRID No. 47070248

SPONSOR: Bayer CropScience AG, Alfred-Nobel-Str. 50, 40789 Monheim, Germany

EXECUTIVE SUMMARY: In an acute dermal toxicity study (MRID 47070248), groups of young Wistar rats (strain HsdCpb:Wu) (5 animals / sex) were dermally exposed to BYH 18636 (Thiencarbazone-methyl) for 24 hours to 10% of the body surface area at doses of 2000 mg/kg bw. Animals then were observed for at least 14 days.

Dermal LD_{50} Males > 2000 mg/kg bw
Dermal LD_{50} Females > 2000 mg/kg bw
Dermal LD_{50} Combined > 2000 mg/kg bw

A apparent dose of 2000 mg/kg body weight was tolerated by male and female rats without mortalities, toxicological effects on weight gain or gross pathological findings.

BYH 18636 (Thiencarbazone-methyl) is of low toxicity based on the dermal LD_{50} which is greater than 2000 mg/kg, resulting in an EPA Toxicity Category III.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. **Test Material:** BYH 18636
   Description: brown liquid
   Lot/Batch #: 2006-003517 (EFIM000617)
   Purity: BYH 18636: 9.98 g/L (Certified by analysis)
   CAS #: CAS No. 317815-83-1

2. **Vehicle and/or positive control:** None

3. **Test animals:** **Rats**
   Species: Wistar
   Strain: HsdCpb:Wu
   Age/weight at dosing: 9-13 weeks / Male: 248-262 g, Female: 203-236 g.
   Source: Harlan/Winkelmann GmbH, 33178 Borchen, Germany
   Housing: Individually caged in polycarbonate cages
   Diet: "Provimi Kliba 3883.0.15 Maus/Ratte Haltung, Kaiseraugst Switzerland" *ad libitum*
   Water: Tap water *ad libitum*
   Environmental conditions:
   Temperature: 22 ± 2 °C
   Humidity: 55 ±5 %
   Air changes: ~ 10 changes /hr
   Photoperiod: 12 hrs dark/12 hrs light
   Acclimation period: 5 days

B. STUDY DESIGN and METHODS:

1. **In life dates** - Start: July 05 2006; End: July 19 2006.

2. **Animal assignment and treatment** - Animals were assigned to the test groups noted in Table 1. Animals were given a single dermal dose of 2000 mg/kg bw BYH 18636 (Thiencarbazone-methyl. One day before treatment the back and flanks of the rats were shorn (approximately 10% of the body surface area). For each dose and animal the required amount of the pure liquid test substance was weighed and applied as uniformly and thinly as possible to the test area, covered with a gauze-layer (6.0 cm x 5.0 cm = 30.0 cm^2) of a "Cutiplast® steril" coated with air-tight "Leukoflex®". The gauze strip was placed on the rat's back and secured in place using "Peha®-Haft" cohesive stretch tape (8 cm x 23 cm) and additionally covered with a "Lomir biomedical Inc rat jacket", which was fastened to ensure that the animals could not ingest the test substance. After 24 hours the dressings were removed and the area was rinsed with tepid water using soap followed by gently patting the area dry.

Clinical observtions and mortality checks were performed several times on the day of application and subsequently at least once daily for an observation period of at least 14 days. Survivors were sacrificed and a necropsy was performed at the end of the study.

3. **Statistics** – Not applicable

II. RESULTS AND DISCUSSION:

A. Mortality is given in Table 1. There were no mortalities at a dose of 2000 mg/kg bw.

TABLE 1. Doses, mortality/animals treated

Dose mg/kg bw.	Toxicological result*	Occurrence of signs	Time of death	Mortality (%)
male				
2000	0 / 5 / 5	2d -- 8d	--	0
female				
2000	0 / 5 / 5	2d -- 8d	--	0

* number of animals which died spontaneously or were sacrificed in moribund state / number of animals with signs of toxicity / total number of animals used per group

B. Clinical observations – The following local signs were observed: partial reddening, partial encrustation, partial swelling and partial formation of scale of the treatment area.

C. Body Weight - There were no toxicological effects on body weight or body weight gain in males.

D. Necropsy - The necropsies performed at the end of the study revealed no particular findings.

E. Applicant's conclusions: The dermal LD_{50} for BYH 18636 (Thiencarbazone-methyl) is greater than 2000 mg/kg body weight for both male and female rats, resulting in an EPA Toxicity Category III.

Reviewer: PMRA
Risk Manager (EPA): 25
Date: July 18, 2008

STUDY TYPE: Acute Inhalation Toxicity - Rat; OPPTS 870.1300; OECD 403

TEST MATERIAL: BYH 18636 (Thiencarbazone-methyl) [Purity: BYH 18636: 9.98 g/L (Certified by analysis); Batch No. 2006-003517 (EFIM000617); brown liquid]

CITATION: Folkerts, A. (2006) BYH 18636 + (Inert Ingredient): Acute Inhalation Toxicity in Rats. Project Number: AT03452, T1077052, M-280714-01-2. Unpublished study prepared by Bayer Ag. 74 p. November 15, 2006. MRID No. 47070247.

SPONSOR: Bayer CropScience AG, Alfred-Nobel-Str. 50, 40789 Monheim, Germany

EXECUTIVE SUMMARY: In an acute inhalation toxicity study (MRID 47070247), groups of young adult HsdCpb:Wu Wistar rats (5 animals / sex / group) were exposed by nose-only inhalation to BYH 18636 (Thiencarbazone-methyl) for 4 hours at a mean maximum attainable concentration of 1.728 mg/L. Animals then were observed for 14 days.

Mortality did not occur at the maximum attainable concentration of 1.728 mg/L. Gross-pathological examinations indicated no observable lesions in the female rats tested, while in the male group 3 out of 5 rats showed discoloration in the lung. At day 1 body weight of the exposed rats were significantly decreased. Thereafter no differences in body weight development between the groups were observed. The rats displayed the following transient clinical signs: Bradypnea, labored breathing patterns, nose: discharge (serous), nostrils: reddened, nose: red encrustions, stridor, piloerection, hair-coat: ungroomed appearance, motility: reduced, limp, tremor. At post exposure day 7 all rats were without clinical signs.

Internationally recognized recommendations such as of SOT (1992) were fulfilled, in regard to the respirability of the aerosol generated, i.e. the MMAD was <4 um (MMAD 3.86 urn, GSD 2.17).

LC_{50} Males > 1.728 mg/L
LC_{50} Females > 1.728 mg/L
LC_{50} Combined > 1.728 mg/L

Based on these results, BYH 18636 (Thiencarbazone-methyl) is classified as being of low toxicity based on combined LC_{50} for both genders, resulting in an EPA Toxicity Category III.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. **Test Material:** BYH 18636
   Description: brown liquid
   Lot/Batch #: 2006-003517 (EFIM000617)
   Purity: BYH 18636: 9.98 g/L (Certified by analysis)
   CAS #: CAS No. 317815-83-1

2. **Vehicle and/or positive control:** Vehicle: The test article was aerosolized as aqueous solution.

3. **Test animals:** **Rats**
   Species: Wistar
   Strain: HsdCpb:Wu
   Age/weight at dosing: 2 months / male: 182-190 g; female: 177-190 g
   Source: Harlan/Winkelmann GmbH, 33178 Borchen, Germany
   Housing: housed singly in conventional Makrolon® Type III_H cages
   Diet: "KLIBA 3883 = NAFAG 9441 pellets maintenance diet for rats and mice; PROVIMI KLIBA SA, 4303 Kaiseraugst, Switzerland" ad libitum
   Water: Tap water *ad libitum*
   Environmental conditions:
   Temperature: 22 ± 2 °C
   Humidity: 40 - 60 %
   Air changes: ~ 10 changes /hr
   Photoperiod: 12 hrs dark / 12 hrs light
   Acclimation period: 5 days

B. STUDY DESIGN and METHODS:

1. **In life dates** - Start: July 17 2006 End: July 31 2006

2. **Exposure conditions** Animals were exposed to the aerosolized test substance in Plexiglas exposure tubes applying a directed-flow nose-only exposure principle. Tubes were chosen that accommodated the animals' size. These tubes were designed so that the rat's tail remained outside the tube to avoid restraint-induced hyperthermia. This type of exposure is preferable to whole-body exposure on scientific and technical reasons (rapid attainment of steady-state concentrations, no problems with regard to test atmosphere inhomogeneities, better capabilities to control all inhalation chamber parameters, easier cleaning of exhaust air, and lower consumption of test substance). Moreover, contamination of the fur can largely be avoided.

3. Animal assignment and treatment - Animals were assigned to the test groups noted in Table 1. Rats were exposed to BYH 18636 (Thiencarbazone-methyl) by nose-only exposure for 4 hours. The appearance and behavior of each rat were examined carefully several times on the day of exposure and at least once daily thereafter. They were weighed on Day 0, 1, 3, 7 and 14 after dosing. Survivors were sacrificed and a necropsy was performed.

4. Generation of the test atmosphere / chamber description:
Time to equilibrium was less than a minute.

Aerosol generation by Nebulization: A modified BGI 3-nozzle Collison nebulizer (Type CN-25 MRE, BGI Inc., Waltham MA, USA) was used in order to attain a high and temporally stable concentration of exposure atmospheres. For aerosolization, the 70% aqueous solution rather than the undiluted test article was used. Pre-tests (without animals) have shown that under such conditions, the output of the nebulizer was maximal. During the course of the exposure period, the reservoir of the nebulizer was exchanged hourly to avoid appreciable changes of the concentration of test article in the reservoir. The temperature was maintained at 25 °C using a digitally controlled thermostat. Conditioned, pressurized air was used for nebulization. The test atmosphere was directly entrained into the inhalation chamber without additional dilution. The aluminum inhalation chamber has the following dimensions: inner diameter = 14 cm, outer diameter = 35 cm (two-chamber system), height = 25 cm (internal volume = about 3.8 l).

Test atmosphere concentration
Nominal concentration: The nominal concentration was calculated from the ratio of the quantity of test article nebulized and the total throughput of air through the inhalation chamber.

Gravimetric evaluation: The test-substance concentration was determined by gravimetric analysis (filter: Glass-Fiber-Filter, Sartorius, Göttingen, Germany; digital balance). The mass collected by the filter was converted to the test item taking into account the concentration of constituents contained in it that are prone to evaporate subsequent to nebulization. The relative proportion of constituents prone to evaporate is determined as follows: aliquots of the test item were added onto glass fiber filters and the filters were allowed to dry under specified conditions (at 70°C drying temperature) over a time period of 180 minutes. During this time course the time of drying was defined at which stable conditions are attained.

Particle size determination
The particle-size distribution was analyzed using a BERNER-TYPE AERAS low-pressure critical orifice cascade impactor (Hauke, Gmunden, Austria). The individual impactor stages had been covered by an aluminum foil and glass fiber filter which were subjected to gravimetric analysis.

The parameters characterizing the particle-size distribution were calculated according to the following procedure:

Mass Median Aerodynamic Diameter (MMAD): Construct a 'Cumulative Percent Found - Less Than Stated Particle Size' table, calculate the total mass of test substance collected in the cascade impactor. Start with the test substance collected on the stage that captures the smallest

particle-size fraction, and divide this mass of the test substance by the total mass found above. Multiply this quotient by 100 to convert to percent. Enter this percent opposite the effective cut-off diameter of the stage above it in the impactor stack. Repeat this step for each of the remaining stages in ascending order. For each stage, add the percentage of mass found to the percentage of mass of the stages below it. Plot the percentage of mass less than the stated size versus particle size in a probability scale against a log particle-size scale, and draw a straight line best fitting the plotted points. A weighted least square regression analysis may be used to achieve the best fit. Note the particle size at which the line crosses the 50% mark. This is the estimated MMAD.

Calculation of Geometric Standard Deviation (GSD): Refer to the log probability graph used to calculate the Mass Median Aerodynamic Diameter. Provided that the line is a good fit to the data, the size distribution is log normal, and the calculation of the Geometric Standard Deviation is appropriate. Note that particle size at which the line crosses the 84.1% mark. Note the particle size at which the line crosses the 50% mark and calculate as follows: GSD = 84.1% mark / 50% mark.

5. Statistics

Necropsy findings: If specific findings occur from the respiratory tract of surviving rats they are evaluated statistically using the pair-wise Fisher test after the R x C chi squared test. The Fisher test was only performed if differences occurred between groups in the R x C chi-squared test or if a frequency value of < 5 was calculated. This procedure was performed in accordance with Gad and Weil (1982). For calculation of the unilateral p value a symmetrical distribution was assumed (p unilateral = (p bilateral)/2).

Body weights: Means and single standard deviations of body weights are calculated. Mean body weights are also depicted graphically as a function of time. Since in acute studies individual group means may differ prior to commencement of the first exposure, the body weight gain was statistically evaluated for each group. For these evaluations a one-way ANOVA (vide infra) is used.

Particle size analysis: The statistical methods used in the evaluation of the particle size distribution are described above.

Physiological data: Data of rectal temperature measurements are statistically evaluated using the ANOVA procedure (vide infra).

Calculation of the LC50: If calculation of a median lethal concentration (LC50) is possible, it is performed by computer (PC) according to the method of Rosiello et al. (1977) as modified by Pauluhn (1983). This method is based on the maximum likelihood method of Bliss (1938). If only 2 pairs of values with greater than 0% lethality and less than 100% are available then the first linear approximation is based on these values and a x2-homogeneity test is not performed. In this case the interpolated concentration at 50% lethality is designated the approximate LC50. Additionally, the moving average interpolation according to Schaper et al. (1994) is used for calculation, if applicable.

Randomization: A computerized list of random numbers served the purpose to assign animals at random to the treatment groups.

Analysis of variance (ANOVA): This parametric method checks for normal distribution of data by comparing the median and mean. The groups are compared at a confidence level of $(1-\alpha) = 95\%$ ($p = 0.05$). The test for the between-group homogeneity of the variance employed Box's test if more than 2 study groups were compared with each other. If the above F-test shows that the intra-group variability is greater than the inter-group variability, this is shown in the Appendix as "no statistical difference between the groups". If a difference is found then a pairwise post-hoc comparison is conducted (1- and 2-sided) using the Games and Howell modification of the Tukey-Kramer significance test. This program was originally obtained from BCTIC.

II. RESULTS AND DISCUSSION:

A. Mortality is given in Table 1. There were no mortalities at a concentration of 1.728 mg/L test substance.

TABLE 1. Concentrations, exposure conditions, mortality/animals treated

Nominal Conc. (mg/L)	Analytical Conc. (mg/L)	MMAD µm	GSD	Mortality (# dead/total)		
				Males	Females	Combined
4.25	1.728	3.86	2.17	0 / 5	0 / 5	0 / 10

B. Clinical observations – The following transient clinical signs were observed in the treatment groups: Bradypnea, labored breathing patterns, nose: discharge (serous), nostrils: reddened, nose: red encrustions, stridor, piloerection, hair-coat: ungroomed, motility: reduced, limp, tremor. At post exposure day 7 all rats were without clinical signs.

C. Body Weight – At day 1 the body weight of exposed rats were significantly decreased. Thereafter no differences in body weights between the groups were observed.

D. Necropsy – There were no observable necropsy findings in the female rats tested, while the male rats showed scattered isolated dark-red foci, light coloration and light colored areas in their lung.

E. Applicant's Conclusions: The acute inhalation LC50 of the BYH 18636 (Thiencarbazone-methyl) for males and females is greater than 1.728 mg/L, resulting in an EPA Toxicity Category III. The NOAEL for males and females is lower than 1.728 mg/L.

Reviewer: PMRA
Risk Manager (EPA): 25

Date: July 18, 2008

STUDY TYPE: Primary Eye Irritation - Rabbit; OPPTS 870.2400; OECD 405

TEST MATERIAL: BYH 18636 (Thiencarbazone-methyl) [Purity: BYH 18636: 9.98 g/L (Certified by analysis); Batch No. 2006-003517 (EFIM000617); brown liquid]

CITATION: Gmelin, C. (2006) BYH 18636 + (Inert Ingredient): Acute Eye Irritation on Rabbits. Project Number: AT03305, T7076590, M-279251. Unpublished study prepared by Bayer Ag. 23 p. September 6, 2006. MRID No. 47070246

SPONSOR: Bayer CropScience AG, Alfred-Nobel-Str. 50, 40789 Monheim, Germany

EXECUTIVE SUMMARY: In a primary eye irritation study (MRID 47070246), 0.1 mL of BYH 18636 (Thiencarbazone-methyl) was instilled into the conjunctival sac of one eye of 3 female young adult albino rabbits (strain Crl:KBL(NZW)BR, Charles River, 88353 Kißlegg, Germany). The eye was not rinsed for at least 24 hours following instillation. The animals were treated in a sequential fashion and observed for 7 days. Irritation was scored by the method of Draize *et al.*[1]

Within 24 hours of test substance instillation in the eyes, positive conjunctivitis and corneal opacity were noted for all three treated eyes, and iritis was noted in 1 out of 3 treated eyes. The overall incidence and severity of irritation decreased with time. All animals were free of ocular irritation by Day 7 (study termination).

According to OECD classification criteria BYH 18636 (Thiencarbazone-methyl) is irritating to eyes with full reversibility within 7 days.

Based on the EPA guidelines, these results are consistent with the criteria for EPA Toxicity Category III (corneal involvement or other eye irritation clearing in 7 days or less).

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

1 Draize, J.H., Woodward, G. and Calvery, H.O. Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. *J. Pharmacol. Exp. Ther.* 1944; 82:377-390.

I. MATERIALS AND METHODS

A. MATERIALS:

1. **Test Material:** BYH 18636
   Description: brown liquid
   Lot/Batch #: 2006-003517 (EFIM000617)
   Purity: BYH 18636: 9.98 g/L (Certified by analysis)
   CAS #: CAS No. 317815-83-1

2. **Vehicle and/or positive control:** None

3. **Test animals:**

Species:	Rabbit	
Strain:	Crl:KBL(NZW)BR	
Age/weight at dosing:	Young adult animals / 2.5 – 2.8 kg	
Source:	Charles River, 88353 Kißlegg, Germany	
Housing:	individually in cage units Metall/Noryl by EBECO	
Diet:	standard diet "Ssniff K-Z" 4mm, approximately 100 g per animal per day	
Water:	Tap water *ad libitum*	
Environmental conditions:	**Temperature:**	20 ± 3 °C
	Humidity:	50 ± 25 %
	Photoperiod:	12 hrs dark/12 hrs light
Acclimation period:	At least 5 days	

B. STUDY DESIGN and METHODS:

1. **In life dates** - Start: August 01 2006 End: August 08 2006

2. **Animal assignment and treatment** On the day before the test, both eyes of each animal were examined including fluorescein examination. Only animals with healthy intact eyes were used. 0.1 mL of the pure liquid test substance BYH 18636 (Thiencarbazone-methyl) was placed into the conjunctival sac of one eye of the first animal after having gently pulled the lower lid away from the eyeball. The lids were gently held together for about one second in order to prevent loss of the test compound. The other eye, which remained untreated, served as control. The eye was not rinsed for at least 24 hours following instillation. If one hour after treatment a severe irritation was not observed, two further rabbits were treated as described. Eye irritations were scored and recorded approximately at 1, 24, 48 and 72 hours post application. If no irritation indices were observed after 72 h, the study was finished. If eye irritations were observed, animals were monitored usually on day 7, 14 and 21 after application until the changes had completely subsided, however for not more than 21 days after application. The degree of ocular lesions was

recorded as specified by DRAIZE and any serious lesions or toxic effects other than ocular lesions were also recorded and fully described.

II. RESULTS AND DISCUSSION:

A. Summary of Irritant Effects:

Animal		24 h	48 h	72 h	Mean scores	Response	Reversible (days)
1	Corneal opacity	2	1	1	1.3	-	7
	Iritis	0	0	0	0.0	-	na
	Redness conjunctivae	3	3	2	2.7	+	7
	Chemosis conjunctivae	3	2	2	2.3	+	7
2	Corneal opacity	2	2	2	2.0	+	7
	Iritis	0	0	0	0.0	-	na
	Redness conjunctivae	3	3	3	3.0	+	7
	Chemosis conjunctivae	3	2	2	2.3	+	7
3	Corneal opacity	2	2	2	2.0	+	7
	Iritis	1	0	0	0.3	-	2
	Redness conjunctivae	3	2	2	2.3	-	7
	Chemosis conjunctivae	3	2	2	2.3	+	7

response:

corneal opacity	: mean scores	< 2 = - ,	≥ 2 < 3 = + , ≥ 3 = ++
iritis	: mean scores	< 1 = - ,	≥ 1 < 2 = + , = 2 = ++
conjunctival redness	: mean scores	< 2.5 = - ,	≥ 2.5 = +
conjunctival oedema	: mean scores	< 2 = - ,	≥ 2 = +

na : not applicable

B. Applicant's Conclusions: According to classification criteria BYH 18636 (Thiencarbazone-methyl) is irritating to eyes with full reversibility within 7 days. There were no systemic intolerance reactions. Based on EPA guidelines, the formulation is in EPA Toxicity Category III since all animals were free of ocular irritation by Day 7.

Reviewer: PMRA
Risk Manager (EPA): 25

Date: July 18, 2008

STUDY TYPE: Primary Dermal Irritation - Rabbit; OPPTS 870.2500; OECD 404

TEST MATERIAL: BYH 18636 (Thiencarbazone-methyl) [Purity: BYH 18636: 9.98 g/L (Certified by analysis); Batch No. 2006-003517 (EFIM000617); brown liquid]

CITATION: Gmelin, C. (2006) BYH 18636 + (Inert Ingredient): Acute Skin Irritation/Corrosion on Rabbits. Project Number: AT03304, T7076589, M-279231-01-2. Unpublished study prepared by Bayer Ag. 23 p. September 6, 2006. MRID No. 47070245

SPONSOR: Bayer CropScience AG, Alfred-Nobel-Str. 50, 40789 Monheim, Germany

EXECUTIVE SUMMARY: In a primary dermal irritation study (MRID 47070245), 3 female young adult albino rabbits (strain Crl:KBL(NZW)BR, Charles River, 88353 Kißlegg, Germany) were dermally exposed to 0.5 mL of pure liquid BYH 18636 (Thiencarbazone-methyl) for 4 hours to an area of 2.5 cm by 2.5 cm in size. Animals then were observed for 3 days. Irritation was scored by the method of Draize *et al* [1].

Moderate erythema was observed in all 3 treated animals for up to 7 days following the exposure.

According to OECD guidelines, BYH 18636 (Thiencarbazone-methyl) is an irritant being totally reversible within 14 days

As moderate irritation was observed at 72 hours post exposure (the calculated primary irritation index is greater than 2 and less than 5), the formulation meets the requirement for EPA Toxicity Category III.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

1 Draize, J.H., Woodward, G. and Calvery, H.O. Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. *J. Pharmacol. Exp. Ther.* 1944; 82:377-390.

I. MATERIALS AND METHODS

A. MATERIALS:

1. **Test Material:** BYH 18636
   Description: brown liquid
   Lot/Batch #: 2006-003517 (EFIM000617)
   Purity: BYH 18636: 9.98 g/L (Certified by analysis)
   CAS #: CAS No. 317815-83-1

2. **Vehicle and/or positive control:** None

3. **Test animals:**

Species:	Rabbit	
Strain:	Crl:KBL(NZW)BR	
Age/weight at treatment:	Young adult animals / 3.0 – 3.2 kg	
Source:	Charles River, 88353 Kißlegg, Germany	
Housing:	individually in cage units Metall/Noryl by EBECO	
Diet:	standard diet "Ssniff K-Z" 4mm, approximately 100 g per animal per day	
Water:	Tap water *ad libitum*	
Environmental conditions:	**Temperature:**	20 ± 3 °C
	Humidity:	50 ± 25 %
	Photoperiod:	12 hrs dark/12 hrs light
Acclimation period:	at least 5 days	

B. STUDY DESIGN and METHODS:

1. **In life dates** - Start: July 25 2006 End: August 8 2006

2. **Animal assignment and treatment** – On the day before test, the fur was shorn on the right and left side from the dorso-lateral area of the trunk of each of the young adult female rabbits. Care was taken to avoid abrading the skin. Only animals with healthy and intact skin were used. 0.5 mL of the pure liquid test substance BYH 18636 (Thiencarbazone-methyl) was applied to the skin of the animal under a gauze patch. The treated skin area was approximately 2.5 cm by 2.5 cm in size. The patch was placed on the dorso-lateral areas of the trunk of each animal and was held in place with non-irritating tape for the duration of the exposure period. Thus, access by the animal to the patch and resultant ingestion of the test substance was prevented. After the exposure period the dressing and patch were removed. The exposed skin area was carefully washed with water without altering the existing response, or the integrity of the epidermis. The surrounding untreated skin served as control.

Due to a possible irritant potential of the test substance, in the first step only one animal was used and three test patches were applied successively to this animal, as described above. The first patch was removed after three minutes. As no serious skin reactions were observed, the second patch was removed after one hour. At this stage the observations indicated that with respect to animal welfare the exposure can be allowed to extend to four hours, therefore the third patch was removed after four hours and the responses were graded one hour later. The test was completed using two additional animals, exposed for four hours.

Based on most recent guidelines the dermal irritation was scored approximately at 1, 24, 48 and 72 hours after patch removal. If no irritation indices were observed after 72 h, the study was finished. If dermal irritation was observed, animals were monitored usually on day 7 and 14 after patch removal until the changes had completely subsided, however for not more than 14 days after application.

The degree of erythema/eschar formation and oedema formation was recorded as specified by DRAIZE and any serious lesions or toxic effects other than dermal irritation were also recorded and fully described.

II. RESULTS AND DISCUSSION:

A. <u>The results are summarized in the table below.</u>

Animal		24 h	48 h	72 h	Mean scores	Response	Reversible (days)
1	Erythema (redness) and eschar formation	3	3	3	3.0	+	14
	Oedema formation	1	1	1	1.0	-	14
2	Erythema (redness) and eschar formation	2	2	2	2.0	+	14
	Oedema formation	0	0	0	0.0	-	na
3	Erythema (redness) and eschar formation	2	2	2	2.0	+	14
	Oedema formation	0	1	1	0.7	-	7

no positive response : mean scores < 2 = -
positive response : mean scores ≥ 2 = +
na : not applicable

B. <u>Applicant's Conclusions</u>: In this study, BYH 18636 (Thiencarbazone-methyl) is an irritant with full reversibility within 14 days according to OECD guidelines. Based on EPA guidelines, the formulation is moderately irritating at 72 hours post exposure, and the data are consistent with the criteria for EPA Toxicity Category III.

Reviewer: PMRA
Risk Manager (EPA): 25

Date: July 18, 2008

STUDY TYPE: Dermal Sensitization - Guinea Pig; OPPTS 870.2600; OECD 406, 429

TEST MATERIAL: BYH 18636 (Thiencarbazone-methyl) [Purity: BYH 18636: 9.98 g/L (Certified by analysis); Batch No. 2006-003517 (EFIM000617); brown liquid]

CITATION: Larsay, M. (2006) BYH 18636 + (Inert Ingredient): Evaluation of Potential Dermal Sensitization in the Local Lymp Node Assay in the Mouse. Project Number: SA 06185, M-279620-01-2. Unpublished study prepared by Bayer Cropscience. 39 p. October 24, 2006. MRID No. 47070244

SPONSOR: Bayer CropScience AG, Alfred-Nobel-Str. 50, 40789 Monheim, Germany

EXECUTIVE SUMMARY: In a dermal sensitization study (MRID 47070244) with BYH 18636 (Thiencarbazone-methyl) at concentrations of 0, 0.5, 1, 2.5, 5% in water containing 1% Pluronic Acid, young female CBA/J mice (4 animals / group) were tested using the method of murine local lymph node assay (LLNA). Positive control 0.25% p-Benzoquinone was spiked in 5% BYH 18636 and 95% of aqueous Pluronic Acid at 1% to ensure appropriate sensitivity under the conditions of this assay. The basic principle underlying LLNA is that skin sensitizers induce proliferation of lymphocytes in the lymph nodes draining the site of chemical application. This proliferation provides a mean for obtaining an objective, quantitative measurement of sensitization. The test measures cellular proliferation as a function of in vivo radioisotope incorporation into the DNA of dividing lymphocytes. The LLNA measures this proliferation in the draining auricular lymph nodes located in the cervical region between test groups and vehicle treated controls.

No mortality and no clinical signs were observed during the study. No cutaneous reactions were observed in the vehicle, reference control or treated groups. The proliferation index values of the test substance were 0.85, 1.7, 2.2 and 1.8 at treatment concentrations of 0.5, 1, 2.5, and 5%, respectively. The proliferation index value of the positive control was 13.3 at a treatment concentration of 0.25% of p-Benzoquinone in 5% BYH 18636 and 95% aqueous Pluronic Acid at 1%.

BYH 18636 (Thiencarbazone-methyl) was found to be a non-sensitizing formulation in the Local Lymph Node Assay.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

1. **Test Material:** BYH 18636
   Description: brown liquid
   Lot/Batch #: 2006-003517 (EFIM000617)
   Purity: BYH 18636: 9.98 g/L (Certified by analysis)
   CAS #: CAS No. 317815-83-1

2. **Vehicle and/or positive control** –

Vehicle: Water containing 1% Pluronic Acid was selected to ensure compatibility with the test substance and maximum wetting of the mouse ears with the maximum possibility of skin penetration of the various formulation ingredients.

Positive control: The positive control substance, p-Benzoquinone, was selected because it is a known sensitizer and it is sufficiently soluble in the formulation. Additionally, the low concentration used was sufficient that it would not interfere with the physical structure of the test formulation.

II. STUDY DESIGN and METHODS:

1. **Animal assignment and treatment** - See Table 1. The ratio of the proliferation in treated groups to that in controls, termed Stimulation Index, is determined and must be at least three before a test substance can be considered as a potential skin sensitizer.

2. **Dose selection rationale** – Concentrations of BYH 18636 in Pluronic Acid as well as the p-Benzoquinone concentration in the formulation were chosen based on results of a screening test, where irritation (measured by ear weight) was observed at concentrations of 10%. Mean ear weight value of 91.1 mg was measured in the group treated at a concentration of 10%, representing an increase of more than 10% compared to control animals (82.0 mg). Therefore, the formulation at the concentration of 10% was considered to be irritant, and concentrations of 0.5, 1, 2.5, 5% were selected in the current test.

3. **Treatment preparation and administration** - Each mouse was topically dosed once daily with 25µl of the formulation using an Eppendorf pipette, to the dorsal surface of each ear. Mice were dosed on Days 0, 1 and 2. On Day 5, animals were placed individually in a retention box, intravenously injected via the tail vein with 250 µl of sodium chloride (0.9%) containing 20 µCi of 3H methyl thymidine and placed in a plastic cage for 5 hours. The lymph nodes from each group of four mice were pooled in a tube containing physiological saline and were disaggregated by crushing with a plastic piston. Cell suspensions were washed with 10 ml of 0.9% physiological saline, centrifuged for 20 minutes at 1800 rpm and the pellets obtained were resuspended in 4 ml of 5% trichloroacetic Acid (TCA) and stored overnight at approximately +4°C. After a final centrifugation, the pellets were resuspended in 1 ml of saline, mixed and then placed for 25 minutes in an Ultrasonic Bath to ensure a thoroughly dispersed suspension. Once prepared, cell suspensions were added to numbered scintillation pots containing 10 ml of scintillation fluid and assayed in a beta-counter.

4. **Statistics** – Not applicable

III. RESULTS and DISCUSSION:

A. **Mortality and clinical signs** - No mortality and no clinical signs were observed during the study. No cutaneous reactions were observed at the treated site for the negative control, positive control or BYH 18636 + Mefenpyr-diethyl OD 70 treated groups.

B. **Body weights** - No significant body weight changes were observed during the study either in the control or in the treated groups.

C. **Disintegrations per Minute/node and Stimulation Index (SI)**

Table 1. Lymph Node DPM Values for all Groups

GROUP	TEST SUBSTANCE(S)	# OF ANIMALS	CONCENTRATION(S) %	DPM/NODE	STIMULATION INDEX (SI)
			DAYS 0-2		
1	Vehicle control	4	0	268	
2	BYH 18636 + Mefenpyr-diethyl OD 70	4	0.5	229	0.85
3		4	1.0	453	1.7
4		4	2.5	601	2.2
5		4	5.0	488	1.8
6	p-Benzoquinone*	4	0.25	3556	13.3

Negative lympho-proliferative responses (SI<3) were noted for BYH 18636 at all concentrations tested. In the positive control group given p-Benzoquinone, a SI value >3 (13.3) was noted. This positive response to p-Benzoquinone demonstrates the validity of this assay under the current condition using the specific test formulation.

D. **Applicant's Conclusions** - There were no confounding effects of irritation or toxicity, so the proliferation values are considered to reflect the sensitization effects of the test and positive control substances. BYH 18636 was found to be a non-sensitizing formulation in the Local Lymph Node Assay in the mouse.

E. **Deficiencies:** The 2003 OPPTS harmonized guidelines state the "LLNA is the preferred method, where applicable." The "where applicable" correlates to the performance parameters in the appendix — the 1999 ICCVAM report. In 1999, ICCVAM validated the method using 209 "single compound compounds" but did not validate the assay for mixtures. The appendix clearly states the LLNA should not be used for metals, aqueous solutions, and mixtures. In January 2008, ICCVAM updated the validation report on LLNA regarding mixtures, metals and aqueous solutions. ICCVAM findings are that when compared to the guinea pig it has a false negative rate of 50%, a false positive rate of 44%, and accuracy rate of 53% in mixtures. Due to these limitations, EPA questioned whether the negative result found in this study is correct. EPA decided to perform a weight of the evidence approach for this joint review chemical by obtaining information on each component (inerts ingredient) in this mixture. After reviewing the

components sensitization potential, EPA determined that most were non-sensitizers and other components were assumed to be below the sensitizing threshold. Therefore, to avoid further animal testing EPA will classify the study as "supplemental" and recommend label language as a non-sensitizer for BYH 18636 (Thiencarbazone-methyl).

ACUTE TOX ONE-LINERS

1. **DP BARCODE:** D339753
2. **PC CODE:** 015804
3. **CURRENT DATE:** 18/JUL/2008
4. **TEST MATERIAL:** BYH 18636 (Thiencarbazone-methyl) [Purity: BYH 18636: 9.98 g/L (Certified by analysis); Batch No. 2006-003517 (EFIM000617); brown liquid]

Study/Species/Lab Study # /Date	MRID	Results	Tox. Cat.	Core Grade
Acute oral toxicity / rat Bayer HealthCare AG AT03394, T9077050 October 23, 2006	47070249	LD_{50} > 2000 mg/kg (females)	III	A
Acute dermal toxicity / rat Bayer HealthCare AG AT03393, T0077051 October 23, 2006	47070248	LD_{50} > 2000 mg/kg (males and females)	III	A
Acute inhalation toxicity / rat Bayer HealthCare AG AT03452, T1077052 November 15, 2006	47070247	LC_{50} > 1.728 mg/L (males and females)	III	A
Primary eye irritation / rabbit Bayer HealthCare AG AT03305, T7076590 September 6, 2006	47070246	Positive conjunctivitis and corneal opacity noted at 72 hours; resolved by Day 7	III	A
Primary dermal irritation / rabbit Bayer HealthCare AG AT03304, T7076589 September 6, 2006	47070245	Moderate irritation was observed at 72 hours	III	A
Dermal sensitization / mouse Bayer CropScience SA 06185, M-279620-01-2 October 24, 2006	47070244	Negative	---	S

Core Grade Key: A =Acceptable, S = Supplementary, U = Unacceptable